SOME LEADERS AND LANDMARKS IN THE HISTORY OF MICROBIOLOGY*

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I am deeply appreciative of the privilege of delivering the annual address of the Society of American Bacteriologists—particularly on this auspicious occasion. I suspect that I owe this honor in part to the fact that I am one of the seven surviving charter members of the Society, albeit the youngest of that historic group; and in part to the circumstance that President Barnett Cohen was the first of my students at Yale and that he desires to get even with me by calling on me to recite.

I have said that this is an auspicious occasion. It is a double anniversary. Meeting here in Baltimore, it is particularly appropriate that we should recall the second President of the Society, William H. Welch who was born in Norfolk, Conn., a century ago.

It was in the year of Welch's birth (1850) that Rayer and Davaine had observed the bacillus of anthrax; and in 1863 Davaine had actually produced the disease by inoculation. It was only in the Seventies, however, that the real importance of bacteriology began to be fully realized by a group of far-sighted pioneers. Europe, and particularly Germany, became the Mecca of young American scientists and Welch studied pathology with Julius Cohnheim, working on acute edema of the lungs. On his return, he established the first pathological laboratory in this country at Bellevue Hospital in New York in 1878. In 1884, he accepted the chair of pathology at the Johns Hopkins, then in the first flush of that pioneer leadership in scholarship which was to transform the whole framework of American higher education. Here, his most outstanding work was in the field of bacteriology as much as in pathology, including the demonstration of the relation of the "Staphylococcus epidermidis albus" toward infections and of the organism which has borne his name for years as *Clostridium welchii*, (in 1892). His principal technical contributions (all between 1888 and 1899) were books on "General Pathology of Fever," "Bacteriology of Surgical Infections" and "Thrombosis and Embolism". It was natural that he should have been one of the founders of this Society and its second President (in 1901).

A second phase of Welch's life was marked by his service as Director of the Johns Hopkins School of Hygiene and Public Health (1918–1926). In this capacity, he exercised a far-reaching personal influence on the whole public health program of this country. In academic and foundation circles, he was consulted about every important move; and his advice was always sound and progressive and statesmanlike.

His third career was as Professor of the History of Medicine at the Johns Hop-

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kins from 1926 to 1931. His leadership in this field was unique and is properly commemorated by the great Welch Medical Library which houses the Johns Hopkins Institute of the History of Medicine, the only institution in this country having adequate funds for large-scale research and teaching in the field of medical history. Under Henry E. Sigerist—and now under R. H. Shryock—this institution has developed a position of commanding influence. I would call the attention of my younger hearers to the fact that as a scientist grows older, his lengthened personal perspective increases his interest in the more fundamental evolution of the whole field of scholarship in which he works. They will do well to prepare themselves for a pleasant and fruitful avocation in later years by an early interest in the history of science.

There were others who made much greater original contributions to bacteriology than William H. Welch. There were others who, as teachers, had as great an influence in the training of students. As a guide and counsellor and inspirer, no one but Osler could be counted as his equal among medical men of his generation. Short, stout and cheerful, he moved through life, with remarkable freedom from the routine burdens which hamper so many. Someone else attended to details while he considered policies and planned for the future. His desk was piled high with unopened letters, so that telegrams were the usual way of communicating with him; but he was somehow always miraculously conscious of any real and vital need. He was a bon vivant, full of the zest for life. When a convention was being held at a very puritanical summer resort, he disappeared for a time and was found, with derby hat set back on his head, and the inevitable cigar in his mouth, on the outskirts of a group of servants who had set up a secret radio set to get the news of a prize fight. His energy was tireless. Traveling in Europe with a much younger colleague, he would put his junior to bed after an exhausting day and go out to walk about the town and see the sights at midnight. He was—as I can testify from personal experience—the kindest and most encouraging and most helpful counsellor of young men; and he was the most trusted advisor of college presidents and foundation executives. The greatest statesman of his time in the fields of medicine and public health.

Welch was, of course, not the only pioneer who lighted the torches of bacteriology on the American continent. Thomas J. Burrill is believed to have first introduced the study of bacteriology into this country at the University of Illinois (1); and in 1877, he discovered the causative organism of pear blight. In the year that Welch came to Bellevue (1878), G. M. Sternberg of the U. S. Army began his study of disinfectants. In 1879, T. M. Prudden was studying and demonstrating bacteria at the College of Physicians and Surgeons in New York; and D. E. Salmon of the Bureau of Animal Industry was investigating the bacteriology of animal disease. In the Eighties, courses in bacteriology began to appear in many of the medical schools and agricultural colleges.

Among these early pioneers in bacteriology, we have three survivors of the Charter Members of this Society, Ludvig Hektoen (born in 1863), F. G. Novy (born in 1864), and H. L. Russell (born in 1866). The work of Dr. Hektoen was commemorated at the first Society of American Bacteriologists Lecture in 1947.

It is appropriate that a word should be said about the two other fathers of bacteriology in America at this time.

Frederick G. Novy[1] was born in Chicago, December 9, 1864, of Bohemian stock and at the age of seven went through the experience of the famous fire initiated by Mrs. O'Leary's cow. Later he was an officer of a High School battalion reviewed by General Grant. While in High School, he was interested in chemistry and microscopy by his Swiss teacher, de la Fontane, and finally worked at night in the Chicago Library amd made enough money to buy a microscope, with which he explored the plankton of adjacent lakes. He took his college course at Michigan, his family moving to Ann Arbor to make this possible; and in 1886 received his bachelor's degree in Chemistry and in 1887, his Master's degree (as an Assistant in Organic Chemistry at the munificent salary of $ 200 a year). Dr. Victor C. Vaughan persuaded him to remain at the University as instructor in Hygiene. He collaborated with Vaughan in a book on Ptomaines and Leucomaines published in 1888.

In working on water analysis, Novy realized that chemistry did not offer a full answer to the problem and he came across "Methoden in Bacteriologie" by Ferdinand Hueppe, a book which I myself remember very well as one of the earliest text-books on this subject. He was fired with the possibilities of the new science and longed to seek for inspiration at the fountainhead. Vaughan thought this an excellent idea and in the summer of 1888 Vaughan and Novy together made a pilgrimage to the Pasteur Institute in Paris and to Koch's laboratory in Berlin, where Novy took a course in bacteriology under Karl Fraenkel. In January, 1889, they gave their first course in Bacteriology at Michigan.

Young Novy won his doctorate of science in 1890 (with a thesis on the Chemistry of the Hog Cholera Bacillus) and his medical degree in 1891 (fast work by modern standards!) In 1891, he married Grace Garwood and they brought up a family of three sons (all physicians) and two daughters (both of whom married physicians). For one who never practiced medicine, Dr. Novy made his contribution to the profession in good measure. He moved steadily on to the rank of Professor of Bacteriology and head of the Department in 1902. In 1904, he served as President of this Society.

Novy's early reserches were largely in the field of organic chemistry but he incidentally discovered an anacrobic organism causing septicemia in rabbits, which was named *Bacillus novyi* by Migula in his Systematic Bacteriology. He ranged over a wide field of microbiology; and perhaps his most important contributions were in the field of protozoology. After failure to cultivate malaria and other intracellular parasites, he succeeded in cultivating trypanosomes isolated from the blood of rats on blood agar (1903), an achievement which attracted much attention in Europe. He produced the first case of experimental infection with *Leishmania*, with a specimen sent to him from Tunis. In 1904, he was able to cultivate *Trypanosoma brucei*. He devoted himself with great intensity to the

[1] For data in regard to the life of Dr. Novy, the speaker is indebted to a manuscript study prepared by William K. Emery, kindly loaned by Professor M. H. Soule, Dr. Novy's successor at Ann Arbor.

study of the spirochetes and his days and nights, spent in the most painstaking microscopic follow-up of the life cycle of these forms, enabled him to correct serious errors made by Schaudinn, and earned him the life-long nickname of "Spi" Novy. He discovered a number of plasmodia and trypanosomes and identified and cultured the spirochete of American relapsing fever (1906) named *Spirochaeta novyi*. One cannot but envy these pioneers their opportunity to range over fields which could be studied only by half-a-dozen different specialists today.

Shortly after World War I, Novy began an important series of studies on "microbic respiration". This work, published in 1925, was a fundamental contribution to bacterial physiology. Mr. W. K. Emery has justly said of him, that he was "the paragon of a scientist, exceedingly particular, meticulous and exacting in every detail, indefatigable in industry, an accurate observer and keen interpreter. His work on the chemistry of bacteria, cultivation of anaerobes, trypanosomes, anaphylaxis and microbic respiration has been not only original but largely basic in these fields."

Dr. Novy was outstanding in teaching, as in research. He was a clear and vivid lecturer with a personality which commanded respect and admiration. Intolerant of carelessness, he was always fair; and his essential dignity was relieved with flashes of delightful humor. He played a major part in elevating Ann Arbor to the position of a leading center of medical education in America. He was a member of the Commission to investigate the plague outbreak in San Francisco in 1901, and a member of the Michigan State Board of Health from 1897–99. He received the degree of LL.D. from the University of Cincinnati (1920) and the University of Michigan (1936). He received the gold medal of the American Medical Association in 1930 and the award of Bausch and Lomb's 250,000th microscope from the American Association for the Advancement of Science in 1936. He was a member of many learned societies in Europe and was a Chevalier of the Legion of Honor.

The third member of the distinguished group whom we honor today is Harry Luman Russell. Born at Ponette, Wisconsin, March 12, 1866, he took his B.S. degree at the University of Wisconsin in 1888. A background for the new science of microbiology had been laid at Madison by William Trelease who had earned his doctorate at Harvard four years earlier by a thesis on the growth of certain bacteria on potato. Trelease's courses at Wisconsin were carried on by E. A. Birge, who, in turn trained young Russell in bacteriology. The apt pupil's first paper dealt with Bacteria of Ice from Lake Mendota (1889).[2]

Between 1890 and 1892, Russell followed the usual novitiate of the day by study abroad, in Koch's laboratory at Berlin, the Pasteur Institute at Paris and the Marine Zoological Station at Naples. On returning to this country, he spent a year with Welch at Baltimore, receiving his degree of Ph.D. in 1892 for a thesis on Bacteria in their Relation to Vegetable Tissue.

After this extended period of eight years of study, Russell began the second

[2] An excellent brief review of Russell's scientific life by E. G. Hastings was published in Papers on Bacteriology and Allied Subjects. By former students of Harry Luman Russell. University of Wisconsin Studies in Science, No. 2, Madison, Wis., 1921.

stage of his career— as teacher and investigator. He was appointed to the faculty at Wisconsin in 1893 and was made full professor in 1897, a post which he held until 1907. These years were highly fruitful, in research and, particularly, in technological leadership. In the course of the fifteen years, from 1893 to 1907, his scientific bibliography includes 107 titles.

In 1892, Koch had prepared tuberculin in the frustrated hope that it might prove a therapeutic agent; but its value as a method of diagnosis was quickly demonstrated. In 1894, Russell tested the herd of the College and found 25 of the 30 animals infected. He at once undertook a vigorous campaign for tuberculin-testing and elimination of infected animals, stumping the State, demonstrating the disease in reacting animals, establishing permanent local outposts for dissemination of knowledge of the disease. Opposition from both veterinarians and farmers was vigorous and progress very slow. In the year 1920, only 67,000 head of cattle were tested in Wisconsin; but by 1930 the number had risen to over a million and a half.

In 1895, a bulletin of the Experiment Station was issued emphasizing the danger of spread of disease (particularly tuberculosis) by milk and a process of holding pasteurization was described and urged. Here the dairy industry was inclined to be cooperative, largely from the desire of avoiding spoilage but, this time, it was the medical profession and the health officials who provided the opposition. The writer can well remember the controversy which persisted on this point, the impassioned denunciation of "cooked filth" and the demand for initial "purity" rather than "repentance." The way of the transgressor is hard; but so is that of the pioneer.

In this bright morning of microbiology, industrial as well as health problems opened up vistas of future progress. Russell, with his distinguished chemical colleague, S. M. Babcock, made basic contributions to our knowledge of the bacterial flora and its role in cheese ripening, including the part of the enzyme galactase in the process. His studies of food spoilage and food preservation led to major improvements in the canning industry; and his laboratory promptly applied the discovery of the nitrogen-fixing bacteria by statewide distribution of these organisms to the farmers of the State. The pre-eminence of Wisconsin in agriculture, in the dairy industries and in the food-preserving industries is, in no small measure, due to the leadership of H. L. Russell.

During this same extraordinarily fruitful period, Russell served as the first director of the State Hygienic Laboratory (1903–1908); and he published books on Dairy Bacteriology (1894), Agricultural Bacteriology (1898), and Public Water Supplies (1901). He served as President of our Society in 1908.

The volume, published in 1921, "Papers on Bacteriology and Allied Subjects by former students of Harry Luman Russell" contains among others, contributions from E. A. Birge, W. D. Frost, B. W. Hammer, H. A. Harding, E. G. Hastings, L. A. Rogers, John Weinzirl and H. A. Whittaker, which gives some measure of Russell's influence as a teacher.

In 1907, he began a third phase of his career as an executive, serving from 1907 to 1931 as Dean of the College of Agriculture and Director of the Agricultural

Experiment Station; and, since 1931, as Director of the Alumni Research Foundation of the University. Of his work as an administrator, a colleague has said: "Dean Russell is recognized everywhere as one of the ablest and most successful agricultural college adminstrators. Under his leadership the Wisconsin institution has won international renown as an agricultural educational institution, and even more as a research center from which scientific discoveries have steadily issued that have well-nigh revolutionized many phases of agricultural science. He has been singularly capable in selecting and holding his staff of scientific workers of outstanding ability and achievement."

This—very briefly—is the story of three of the founders of American microbiology, typical representatives of the pioneers who laid the basis for all future progress on this continent. T. J. Burrill, T. Mitchell Prudden, D. E. Salmon, G. M. Sternberg, and W. H. Welch, in the '70's; A. C. Abbott (Philadelphia), H. M. Biggs (New York), E. A. Birge (Wisconsin), T. M. Cheesman (New York), H. W. Conn (Storrs, Conn.), H. T. Detmers (Ohio), H. C. Ernst (Boston), Henry Formad (Philadelphia), B. Homes (Chicago), F. G. Novy (Michigan), L. H. Pammel (Iowa), W. T. Sedgwick (M.I.T.), Theobald Smith (George Washington University), V. C. Vaughan (Michigan) and J. E. Weeks (New York), in the '80's, are listed by Gorham (1) as being on this distinguished honor roll.

Many of these pioneers, like Welch, Novy and Russell, themselves crossed the ocean (a much rarer experience in that day than now) to seek inspiration in Berlin and in Paris. All of them drew their inspiration from the work of Pasteur and of Koch. It was a thrilling period in the history of our science— the revelation as "the science of the infinitely little"— the sudden opening of a whole new world of organic life, fraught with the widest implications for the future welfare of mankind. No wonder this prospect caught the imagination of the most courageous and creative minds. It is not surprising that the young men who saw the vision of this gleam included so many of outstanding qualities of leadership. Our science got off to a good start.

What was behind this sudden flowering of microbiology is a familiar chapter in the history of science.

It began, of course, with Antony van Leeuwenhoek, the lens-maker and microscopist of Delft. With a simple lens of his own construction, he had a marvelous time exploring the microscopic universe, which he described in 375 letters to the Royal Society of London and 27 to the French Academy of Sciences. He gave us clear records of many protozoa and his letter to the Royal Society, dated September 14, 1683, contains the first drawing of bacteria (rods, cocci and spirilla) in a suspension of tartar scraped from the teeth, with the delightful comment "I saw with wonder that my material contained many tiny animals which moved about in a most amusing fashion; the largest of these showed the liveliest and most active motion, moving through the water or saliva as a fish of prey darts through the sea."

The fascinating observations of the Dutch microscopist led to no further important advances for a century and a half. The compound microscope was gradually developed during this period; but its use was limited by the fact that with more convex lenses the light rays of different wave lengths were separated creating a colored rim which made definition defective. The discovery that a combination of concave lenses of flint glass with convex lenses of crown glass would eliminate this "chromatic aberration" was perhaps first applied by Amici of Modena in 1812. By 1835, the application of this principle had made the compound microscope an instrument of major usefulness. There are few more striking examples of the far-reaching scientific repercussions of a relatively simple improvement in a physical instrument. As Sedgwick (2) says, "Almost immediately results of capital importance were reached, for in 1837 an Italian investigator, announced the discovery that muscardine, a contagious disease of silkworms, previously not understood, is really due to a parasitic fungus. Two years later the still more startling discovery was made by Schoenlein that favus or "honeycomb" of the human scalp, a disease long known, but never understood, is really due to a parasitic fungus growing at the roots of the hair. At almost the same moment botanists discovered that yeast, hitherto regarded as a mysterious 'ferment' is also a microscopic fungus."

The significance of such discoveries of living organisms in the presence of fermentation and disease depended, however, on a clear distinction between the living and the non-living world; and this distinction had not been clearly established until the period under discussion. It had been believed in classical times that worms and frogs could be spontaneously generated in river mud or by organic decay (the theory of abiogenesis); and this same view had persisted with regard to lower forms of life. It had been challenged by Redi at Florence in the Seventeenth Century and by Spallanzani in the Eighteenth. Cagniard de Latour (1835–38) described the yeast plant and attributed fermentation to the action of its living cells. "The leaders of German chemistry (Berzelius, Liebig and Wöhler), however, received these communications with scorn, and Liebig actually published in Liebig's *Annalen* an anonymous, mock-scientific article describing the observation with a wonderful new microscope of yeast cells shaped like stills with streams of sugar going in at one end and alcohol and carbon dioxide going out the other—which has been justly described as the most remarkable contribution which ever appeared in a serious scientific periodical"(3).

The powerful opposition of Liebig, the Pope of European chemical science in the middle Nineteenth Century, was only overcome by the experiments of Schulze, Schwann, and Schroeder and von Dusch. Spallanzani had shown that no fermentation and no generation of microbes occurred in flasks of decomposable matter which had been immersed in boiling water and their necks sealed off. But, "in view of growing recognition of the necessity of oxygen for the life process, might not Spallanzani's failure to obtain growth have been merely due to the exclusion of oxygen from his sealed flasks? To answer this question, Franz Schulze in 1836 and Theodor Schwann in 1837 made the experiment in flasks which were freely connected with the atmosphere by means of open, but coiled, tubes. In the trap of this inlet sulphuric acid was placed; or the trap was kept red-hot by a flame. As the flask cooled, oxygen bubbled in through the acid or passed in through the heated section; and air thus treated yielded no growth in the flask. Stubborn opponents then claimed that the acidified or calcined air had been so changed that it would no longer support life. Finally, in 1854, H. Schroeder and T. von Dusch, replaced acid or heat in the inlet tube by a filter of cotton wool and still obtained sterile solutions" (3).

It was the perfection of the achromatic objective and the demonstration of biogenesis which made possible the epoch-making researches of Pasteur, a story too familiar to require retelling. He demonstrated beyond doubt the microbic cause of fermentation (1857); he further demolished the theory of abiogenesis (1862)[3]; he elucidated the role of microörganisms in the spoilage of wine (1863) and beer (1871); he described a microbic disease of silkworms (1865); he did pioneer work on anthrax and chicken cholera (1877); and established the principle of preventive vaccination (1880).

Meanwhile, Ehrenberg in 1838 had been classifying microörganisms and Ferdinand Cohn of Breslau (1854) improved Ehrenberg's classification and laid a solid basis for systematic bacteriology. In 1863, Davaine produced anthrax by inoculation of the germ. In 1866 Rundfleisch described the organisms of pyemia; in 1873 Obermeier discovered the spirillum of relapsing fever. In 1877 Pasteur found the causative agent of malignant edema. In 1879 came the infective agent of leprosy (Hansen and Neisser); and of gonorrhea (Neisser); in 1880, of pneumonia (Pasteur, and simultaneously, Sternberg in this country); and of fowl cholera and staphylococcus infection (Pasteur).

In the 1870's, the center of inspiration in the new science of bacteriology began to shift from France to Germany. Always, Paris had been strong on principles and ideas, Berlin on techniques. The two most important technical advances in microbiology (after the achromatic objective) were the introduction of the staining technique by Weigert (1871–75), and the use of solid culture media for isolation of bacteria by Koch (as a tube method in 1875 and a plate method in 1883). The difficulty of establishing absolute priority in such matters is illustrated by the fact that Vittadini and other botanists had grown microörganisms on gelatin as early as 1852 and that Klebs had recommended its use for bacteria in 1873. It was, however, Koch's paper of 1876–7 which actually brought this procedure into use. It was discovered by observation of colonies which spontaneously developed on slices of potato in the laboratory; and the method of plating on solid media quickly replaced Pasteur's cumbrous dilution method for the isolation of pure cultures.

In 1882, Koch described the bacillus of tuberculosis in a paper which has always seemed to the writer the most outstanding single contribution in the history of bacteriology—perhaps equalled only by William Harvey in any medical field. The paper includes demonstration of three major facts: (a) the presence of the tubercle bacillus (as proved by staining) in tubercular lesions of various organs of men and animals; (b) the cultivation of the organism in pure culture on blood

[3] It was probably fortunate that Pasteur and his predecessors did not encounter highly heat-resistant spores in their experiments, or those experiments might have failed.

serum; and (c) the production of tuberculosis at will by its inoculation into guinea pigs.

Here was a disease which was not even recognized as a specific entity[4] and of whose causation there was—in spite of Villemin's experiments—no accepted theory. Before the presentation of this paper, nothing was definitely known about the etiology of tuberculosis; after its presentation, the whole picture was clear. In a memoir which occupies seventeen pages in Koch's collected works, there is not a single error, except the interpretation of certain structures in the cell as spores. Furthermore it contains practically everything we now know about the bacteriology of the tubercle bacillus except the difference between the human and bovine types and the recent knowledge of the chemistry of the tubercle bacillus (perhaps also its filtrable stage, if such a stage really exists).

If one may imagine initiating a class in bacteriology into the technique of the science by asking them to make pure cultures of the tubercle bacillus, one gains some conception of the difficulty of the task accomplished by Koch in 1882.

The influence of this paper was as phenomenal as its quality. Pasteur, up to 1877, had worked with no animal host higher than the silkworm; and the studies of Davaine, Koch and Pasteur on anthrax had related to a malady which—while it did affect man—was primarily of veterinary interest. In tuberculosis, however, Koch was dealing with perhaps the greatest plague affecting the human race at that time. His elegant technique applied to such a central problem was electrifying in its effect.

By the early '80's, then the field of microbiology was in truth ripe for the harvest. During the last fifteen years of the Nineteenth Century, when our eager students from America brought back the torch from Paris and Berlin, every one of the varied specialties of our science became well established.

In the area of medicine, the causes of most of the important diseases were identified during this period. In the 80's came the germs of typhoid fever, malaria, staphylococcus infection, tuberculosis, streptococcal infection, glanders, cholera, infectious conjunctivitis, erysipelas, diphtheria and tetanus, the colon bacillus, the meningococcus and the paratyphoid organisms. In the '90's, the gas bacillus, the plague bacillus and the dysentery bacillus were identified. Almost as important as the definition of a given case of disease by bacteriologic methods, was the demonstration of the great significance of the well carrier—by Koch for cholera in 1893, and by William H. Park of New York for diphtheria in 1894. Only through recognition of the important role of the well carrier was it possible to establish the germ theory of disease on a sound foundation.

The control of host immunity by the use of an attenuated vaccine had, of course, been introduced by Jenner for small-pox in 1798; but this remained for nearly a century an isolated phenomenon, which no one thought of applying in other diseases. It was Pasteur who actually developed the theoretical concept of protection against disease by the inoculation of a weakened strain of the causa-

[4] Of the two leading medical schools of New York City at this time, one taught that tuberculosis was a single disease, the other that the development of tubercles was merely a symptom of various diseases.

tive organism (discovered through the chance attenuation of a laboratory culture of chicken cholera); and in 1881, he made his daring and brilliant demonstration of protection of cattle against anthrax at the farm of Pouilly-le-Fort, one of the most dramatic episodes in the history of public health. Ten years later, in 1890–93, the complementary principle of protection by the use of antitoxic sera was developed by Behring and Kitasato in Berlin. Meanwhile, the concept of phagocytic immunity had been developed by Metchnikoff in 1884. In 1896 came the Widal test and—as a result of independent studies in England, France and Germany—vaccination against typhoid fever took its place, along with small-pox vaccination and diphtheria immunization, as a practical public health procedure. It was Park's New York City Laboratory which, in 1893, became the inspiration for the applications of medical bacteriology and serology in the United States.

In sanitary bacteriology, similar progress was taking place. Burdon-Sanderson in England in 1871 demonstrated the presence of bacteria in water; and Miquel at Paris in 1880 developed the first exact methods for enumerating them. In 1885, Percy Frankland used Koch's procedures in a study of London water supplies and in 1887 Plagge and Proskauer reported on the bacterial purification effected by the filters of Berlin. In this same year, the establishment by the Massachusetts State Board of Health of its experiment station at Lawrence gave a vigorous stimulus to the science of water and sewage treatment. In 1888, the first municipal public health laboratory was opened in Providence. In the Nineties, under the leadership of Wyatt Johnston of Montreal, the American Public Health Association began organized committee study, for the development of standard methods of water analysis. In 1892, Theobald Smith devised the gas fermentation tube for the quantitative estimation of colon bacilli.

Pasteur demonstrated the presence of bacteria in the air in 1860. Atmospheric microörganisms were studied by Maddox and Cunningham in the '70's and by Cohn, Pasteur and Miquel in Europe and Sedgwick in this country in the '80's. Interest in this subject was aroused in England by Tyndall's "Essays on the Floating Matter of the Air" (1881); and, in this country by T. M. Prudden's "Dust and its Dangers" (1890).

Veterinary microbiology has an even longer history. Rayer and Davaine in 1850 and Pollender in 1855 observed the anthrax bacillus, and Davaine in 1863 produced the disease by inoculating cattle with blood containing the rods he had recognized as the cause. In 1876, Koch's classic contribution on this subject established the relationship beyond any doubt. In 1878, Bollinger identified the cause of actinomycosis, and in 1880 Griffith and Evans described the first protozoan (a trypanosome) identified as a cause of animal disease. In 1893, American microbiology made its first major contribution, in the form of Smith and Kilborne's monograph on Texas Fever—one of the most imaginative and exhaustive studies of any disease in the history of public health and the foundation of all later work on the animal host and the anthropod vector.

The field of milk bacteriology, which was to develop so extensively in later years, was opened up by H. W. Conn in 1889, and continued its progress under Russell, as noted in an earlier paragraph. The first bacteriological studies of market milk in this country were made by Sedgwick and Batchelder in 1892—revealing an average of 4,500,000 colonies per milliliter in milk on sale at grocery stores. It was this report which initiated the first active campaign for milk pasteurization.

The problem of soil bacteriology also attracted attention in the very early days. Schloesing and Müntz in France demonstrated in 1877 that nitrification in soils must be due to microbic action, since it was prevented by heat treatment or the presence of antiseptic substances. Winogradsky in 1890 first isolated an unmistakable nitrifying organism by the dilution method and his results were quickly confirmed at the Lawrence Experiment Station. Between 1896 and 1899, Winogradsky, Beijerinck and Omelianski obtained pure cultures of nitrifying organisms on various solid media.

The role of the root nodules in nitrogen-fixation was established by Hellriegel and Wilfarth in 1886 and confirmed in this country by Atwater and Woods in 1890. Beijerinck isolated the bacteria concerned in 1888. In 1895, Winogradsky first demonstrated the role of bacteria in the process of nitrogen fixation in the soil itself. The first bacteriologist (Atwater being a chemist) to publish on the subject of soil bacteriology in the United States was F. D. Chester (1898).

In the study of plant diseases, the role of American microbiologists has been of notable importance. As early as 1880, T. J. Burrill at Illinois discovered and described the bacillus causing pear blight. The organism of the yellow disease of hyacinths was discovered in Europe by Wakker in 1883 and that of olive knot in France in 1886. Both were later fruitfully studied by Erwin F. Smith in our own Bureau of Animal Industry. The cause of black rot of cabbage was discovered by Pammel at Iowa in 1895 and more fully worked out by Erwin Smith (1897) and by Russell at Wisconsin (1898).

Industrial microbiology got off with the best start of all, in Pasteur's work on fermentation (1857), diseases of wine (1863), diseases of silkworms (1865) and microörganisms in beer (1871). These studies were all directly concerned with industrial problems relating to the fermentation and silk industries and led also to fundamental discoveries in the vinegar industry. After Pasteur, however, progress along these lines was less spectacular during the Nineteenth Century. The work of Wood on the bacteriology of tanning was perhaps the most important contribution of American microbiology in this field.

I have said enough to make clear the astounding progress of microbiology in the period between 1880 and 1900. Dr. T. M. Prudden used to relate how he was wakened from his morning sleep by the arrival of young Welch to share the exciting news of Koch's paper on the tubercle bacillus, which completely revolutionized the current views of medical science with regard to that disease. I think it was Osler who once said that during this period new discoveries came with the frequency of corn popping in a pan. Each year, new vistas opened; and the views revealed were enthralling in their scope and magnitude. Those of us who began our careers in bacteriology at the end of this period were indeed called to action by the light of a glorious dawn.

By 1899, when this Society was organized, the sun was well over the horizon.

The crops of knowledge which have been garnered by its members during the past half century are far too rich and far too various, to be catalogued in one—or in a dozen—addresses. In the few minutes left at my disposal, I can only remind you of certain of the major advances which have had most far-reaching theoretical significance.

The microbiologist is, after all, a *biologist.* He deals with living organisms; and the fundamental basis of biology is normally morphology. It is true that in the virus field, ingenious indirect experimentation revealed many of the characteristics of what may today be properly called living units before those units had been recognized by the human eye. In general, however, our knowledge of yeasts and molds and bacteria and protozoa rested first on the revelations of the microscope. The achromatic objective, as we have seen, opened the door to the great advances of a century ago. The recognition of rods, cocci and spirilla, of spores and capsules, and flagella, dates far back in the history of bacteriology. So do the specific chemical stains whose action serves to translate subtle chemical differences into a definitive picture under the microscope, such as Gram's stain (1884) which has demonstrated such remarkable correlations with physiological behavior and with the taxonomic relationships of the bacteria. In this field of morphology, there is one major landmark of the present century, the application of the electron microscope, applied to bacteria by Morton, by Van Borries, Ruska, and by Krause, in 1937 and 1938; and employed more intensively in this country by Stuart Mudd and his associates, by Will, Packard and Kearing and by Morton and Anderson between 1941 and 1943. This insturment has revealed so much about the internal structure of the bacteria and about the morphology of the rickettsias and the viruses as to rank second only to the achromatic objective as a landmark in the history of microbic morphological research.

A second major essential in biological science is taxonomy, since it is impossible to study organisms intelligently without a sound understanding of their mutual phylogenetic relationships. When this Society was founded, we had rough but useful check lists of known bacterial types of which the most exhaustive was Migula's *System der Bakterien* (1897). In this country, F. D. Chester's *Manual of Determinative Bacteriology* appeared in 1901. In 1909, Jensen presented the first attempt at a classification, based not on morphology but on physiological behavior. In this field, we can fairly claim that American bacteriologists have been in the lead. In 1920, a Committee of this Society[5] after three years of study presented a report on the Characterization and Classification of Bacterial Types which was the basis for the classic work of D. H. Bergey first published in 1923, and in its latest edition still the standard work of reference in this field.

Taxonomy is essential to give us a picture of the general pattern of living organisms as we find them in a given stage of evolution. The picture, however, is a changing one, particularly in the unicellular world. The study of mutation and of genetics in a broad sense is therefore another area of vital importance. Various European bacteriologists, between 1906 and 1910, noted the presence

[5] C.-E. A. Winslow, Chairman, J. Broadhurst, R. E. Buchanan, C. Krumwiede, L. A. Rogers and G. H. Smith.

of papillae on colonies of coliform bacteria which represented mutants exhibiting specific fermentative powers. Barker in 1913 and Jordan, in 1915 traced the persistence for some years of mutants of this type arising from a single cell culture originally lacking the particular ferment involved. A striking stimulus to the study of this subject was provided when Arkwright in 1921 described the development and persistence of rough and smooth colony types. Hadley's impressive monograph on this subject appeared in 1927. The bacteriologist of today can scarcely realize how this phenomenon had been overlooked; yet it was. In my own Master's thesis in 1899 I counted thousands of plates of typhoid colonies. I suppose that most of those plates had rough and smooth colonies; but I never knew it. It is one of the great pitfalls of science that we so often see only what we expect to see—not what is really there.

One of the major changes in microbiology during the Twentieth Century has, of course, been the broadening of our field to include minute forms of life such as the rickettsias, and the "viruses." The members of this Society in 1899 knew about bacteria and yeasts and molds and protozoa; but that was essentially the limit of their knowledge. It is true that as early as 1892, Iwanowski had demonstrated that the mosaic disease of tobacco could be transmitted by the filtered juice of infected plants; and in 1897–98, Loeffler and Frosch provided a similar demonstration with regard to foot and mouth disease of cattle; but these were exceptional experiences which only slowly influenced scientific theory in general. An important further step was taken when Twort in 1915 first described the analogous phenomenon of the bacteriophage.

At about this same time, the study of the rickettsias was placed upon a firm basis. Ricketts in 1909 and Ricketts and Wilder in 1910, described "bacillary bodies" in Rocky Mountain fever and typhus fever. Da Rocha Lima named *Rickettsia prowazeki* in 1916 for two pioneers who had both fallen victims to the germs they studied; and Wolbach and his associates in 1922 clinched the evidence with regard to the causative agent of epidemic typhus.

Up to a decade ago, bacteriological literature was replete with arguments as to whether filterable viruses were "living" or "non-living". The dependence of viruses and rickettsias on living cells of the higher organisms which they attack was the chief argument against their recognition as, themselves, organisms; but, after all, men and animals are ultimately dependent for their existence on the plant world which snares the energy of the sun; but we do not deny to them the attribute of life. The electron microscope makes it clear that small bacteria, rickettsiae and viruses form a complete series from the morphologic standpoint. Where "life" begins is a terminological concept which may be left to the philosopher.

Far more significant than any advances in morphological or taxonomic science has been the growth of our knowledge with regard to the physiology of micro-organisms and, particularly, with respect to the processes of organic chemistry and physical chemistry involved. When I began my career as a practicing bacteriologist, the culture tube and the microscopic slide were our chief tools of research. When I turned the editorship of the *Journal of Bacteriology* over to the capable hands of J. M. Sherman in 1944, the complexities of chemical techniques involved had become so great that many of the papers presented were far beyond the scope of my training and experience. This was, of course, all to the good, since the resolution of "biological" problems into "chemical" phenomena, and the understanding of "chemical" processes in terms of "physical" laws is part of the general process of simplification and generalization which is the essence of scientific advance. Perhaps all such processes will some day be interpreted as special cases of Einstein's simple laws.

Be that as it may, you men and women of the younger generation are adding each year, fruitful information as to the varied and complex organic and inorganic compounds and elements which stimulate (or inhibit) microbic growth and development, information which is not only of immediate practical importance but which opens the way to a deeper understanding of the processes of life itself.[6]

The study of specific organic and inorganic building stones necessary for microbic life, of essential enzymes, and of specific inhibitors of the life process, has made astounding advances, which have led to the development of microbiological assay procedures, and which promise to throw light on the metabolism of more complex and less easily studied forms of life.

One of the most outstanding advances in bacterial physiology has been recognition of the basic importance of oxidation-reduction reactions in the processes of organic life. Here the work of W. M. Clark has been of special importance. One of the most fruitful papers which has ever come out in the *Journal of Bacteriology* was the contribution of Clark and Lubs on pH, its measurement and its significance in our second volume for 1917.

While chemistry and physics are basic, however, there is still much to be learned in regard to those phenomena which result from such relatively simple processes on the more complex biological level. In this field, the study of the bacterial culture cycle still has fascinating possibilities. In a given medium, the growth and death of individual cells produces a sort of societal unit which has characteristics closely resembling those of a multicellular organism, as pointed out by R. E. Buchanan and E. I. Fulmer (4). The lag period (including a stationary phase and one of accelerating growth), the period of maximum logarithmic growth and the third period of gradual decline present a picture closely resembling the growth and death phases of higher forms of life. It is of interest to note that recent studies of this process in the bacterial culture cycle have shown promise of throwing real light on the problems underlying the causation of the cancer process in man.

In this area of microbiology the work of what has been called by C. B. van Niel (5) the "Delft School" has been of primary importance. Many of you heard Dr. van Niel's notable address at last year's meeting in Cincinnati. More of you, I trust, have read it or will read it. You will recall that—more than two and a quarter centuries after Leeuwenhoek first described bacteria—M. W. Beijerinck founded a new "Delft School" with his emphasis on the enrichment culture and

[6] For a fascinating analysis of the borderland between biology and physics, see M. Delbrück, "A Physicist Looks at Biology", Trans. Conn. Acad. Arts and Sciences, 1949, **38**, 173.

its significance as a tool in the study of microbial ecology. He and his pupil, A. J. Kluyver, established the discipline of "comparative biochemistry" which has opened up some of the most fruitful avenues of present day research.

Finally, of course, the microbiologist is intensely interested in those of the end products of microbic netabolism which are of immediate significance—for good or for ill—in their influence on the practical conduct of human life. Pasteur studied the fermentation of wine and beer and of vinegar because the yeast cell produced alcohol and the mycoderma produced acetic acid. Roux and Behring were interested in the Klebs-Loeffler bacillus because it formed diphtheria toxin. To leap over almost a century, the most dramatic recent event in the field of medicine has been the development of antibiotics through the discovery of penicillin, and streptomycin.

Here, as in so many other phases of the history of bacteriology, the key phenomena had long been before us—if our minds had been as open as our eyes. John Tyndall (6) in 1881 reported that "The turnip-infusion, after developing in the first instance its myriadfold Bacterial life, frequently contracts mould, which stifles the Bacteria and clears the liquid all the way between the sediment and the scum. Of two tubes placed beside each other, one will be taken possession of by Bacteria, which successfully fight the mould and keep the surface perfectly clean; while another will allow the mould a footing, the apparent destruction of the Bacteria being the consequence. This I have proved to be the case with all infusions, fish, flesh, fowl, and vegetable. At the present moment, for example, of three tubes containing an infusion of sole, placed close together in a row, the two outside ones are covered by a thick tough blanket of mould, while the central one has not a single speck upon its surface. The Bacteria which manufacture a green pigment appear to be uniformly victorious in their fight with the *Penicillium.*" (The green fluorescent bacteria, it will be recalled are gram-negative.) Think what hundreds of thousands of deaths from pneumonia could have been avoided, if this lead had been followed up.

It was nearly half a century later, in 1929, however, that A. Fleming again made the chance observation that mould contaminations on plates of staphylococcus cultures exerted a specific antagonistic action and postulated during the next three years the existence of the first antibiotic, penicillin. It was 1940 before Chain and his associates actually developed the application of this discovery and led, in 1941 (in the United States) to its large-scale development.

Three years later, in 1944, S. A. Waksman and his associates described streptomycin, which has somewhat the same specific antibiotic power against the gram-negative organisms which is exercised by penicillin against their gram-positive congeners.

This is a good example with which to close an address, already far too long. There could be no clearer demonstration of the importance of microbiology as an independent science than the fact that the control of pneumonia in human beings came from the observation of an antagonistic action of accidental mould contaminations in the laboratory; and the fact that a specific for control of diseases due to gram-negative parasites of man was discovered by a soil mycologist.

Microbiology is not a technical tool for the doctor, the agriculturalist or the engineer. It is a basic biological science; and it may well be claimed that it has rendered greater service to mankind than any other science of this class. This service has been made possible because it is a basic science; and its fruits in the future will depend on the soundness and independence of the discipline you represent.

The objects of the new society were stated, in the first constitution, to be "the promotion of the science of bacteriology, the bringing together of American bacteriologists, the demonstration and discussion of bacteriological methods, and the consideration of subjects of common interest." "Embodied in this simple declaration" (as Dr. Cohen has said) " is the broad vision held by the founders that 'bacteriology' was destined to represent a fundamental discipline and a liberal science; and that bacteriologists had an embracing and fundamental common interest irrespective of the particular field of study or application that happened to engage their attention." This was made abundantly clear by Professor Sedgwick in his presidential address in 1901 (7); and elaborated in a statement, published in 1902, on the scope and function of the Society and accepted as its basic policy.

You have behind you the heritage of a half-century of brilliant progress. You have before you a limitless horizon for the future.

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